(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
1 August 2002 (01.08.2002)

PCT

(10) International Publication Number
WO 02/059132 A1

(51) International Patent Classification[7]: C07F 7/02, C07D 317/00, 319/06, 407/00, 413/00, C07C 45/00, 47/56

(21) International Application Number: PCT/US02/02338

(22) International Filing Date: 28 January 2002 (28.01.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/264,642 26 January 2001 (26.01.2001) US

(71) Applicant *(for all designated States except US)*: **VIROPHARMA INCORPORATED** [US/US]; 405 Eagleview Boulevard, Exton, PA 19341 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **RYS, David, J.** [US/US]; 224 Ripka Street, Apt. #2, Philadelphia, PA 19127 (US). **NITZ, Theodore, J.** [US/US]; 473 Kulp Road, Pottstown, PA 19465 (US).

(74) Agents: **HAGAN, Patrick, J.** et al.; Dann, Dorfman, Herrell and Skillman, P.C., 1601 Market Street, Suite 720, Philadelphia, PA 19103 (US).

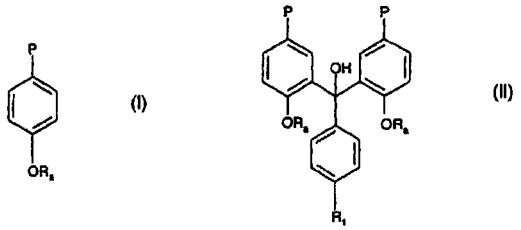
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

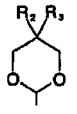
(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

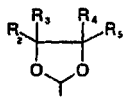
Published:
— *with international search report*

[Continued on next page]

(54) Title: INTERMEDIATE COMPOUNDS USEFUL FOR MAKING ANTIVIRAL COMPOUNDS







(57) Abstract: Novel compounds of Formula I and Formula II (below): formula (I) wherein R_a is selected from the group consisting of $-CH_2-OCH_3$, $-CH_2-OCH_2CH_3$, $-CH(CH_3)OCH_2CH_3$, $-CH_2-OCH_2CH_2-OCH_3$, $-CH_2OCH_2CH_2-Si(CH_3)_3$, and formula (II); R_1 is a radical selected from the group consisting of hydrogen, halogen, perfluoroalkyl, nitro, carbalkoxy, carboxamide, carboxamidoalkyl, alkyl, cycloalkyl, alkoxy, alkoxyalkyl, alkoxy-C_2-C_6-alkoxy, alkylsulfinyl, alkylsulfonyl, sulfonamide, cyano, amido, dialkylamino, OR_a, or a heterocyclic radical selected from the group consisting of morpholinyl, piperadinyl, pyrrolidinyl, or an N-substituted piperazinyl, said piperazinyl substituents selected from an alkyl group, the point of attachment of said heterocyclic radical is at a nitrogen atom; P is a protected formaldehyde group such as: formula (III) or formula (IV) wherein R_2, R_3, R_4 and R_5 are independently selected from the group consisting of hydrogen or alkyl. The compounds are useful for making antiviral agents.

WO 02/059132 A1

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERMEDIATE COMPOUNDS USEFUL FOR MAKING ANTIVIRAL COMPOUNDS

FIELD OF THE INVENTION

The present invention relates to novel intermediate compounds which are useful for preparing antiviral compounds. The invention also relates to the methods of making the intermediate compounds and methods of preparing antiviral compounds from the intermediate compounds.

BACKGROUND OF THE INVENTION

The *Pneumovirinae* subfamily of the *Paramyxoviridae* family consists of pneumoviruses that cause significant disease in humans and a number of animal species including cattle, goats, sheep, and mice, and in avian species.

Human respiratory syncytial virus (RSV), the prototypic member of the pneumovirus group, is the major pediatric viral respiratory tract pathogen, causing pneumonia and bronchiolitis in infants and young children. RSV disease is seasonal, with outbreaks in the U.S. typically beginning in November and continuing through April. During these yearly epidemics, approximately 250,000 infants contract RSV pneumonia, and up to 35% are hospitalized. Of those hospitalized, mortality rates of up to 5% have been reported. Children with underlying conditions such as prematurity, congenital heart disease, bronchopulmonary dysplasia and various congenital or acquired immunodeficiency syndromes are at greatest risk of serious RSV morbidity and mortality. In adults, RSV usually causes upper respiratory tract manifestations but can also cause lower respiratory tract disease, especially in the elderly and in immunocompromised persons. Infection in elderly and immunocompromised persons can be associated with high death rates. Natural infection with RSV fails to provide full protective immunity. Consequently, RSV causes repeated symptomatic infections throughout life.

The pneumoviruses of animals and avian species are similar to the human virus antigenically, in polypeptide composition and in disease causation.

Attempts to develop vaccines for RSV are ongoing, but none have yet been demonstrated to be safe and efficacious. Vaccine development has been shadowed by adverse reactions exhibited by the initial formalin-inactivated RSV vaccine introduced in the late 1960s. Immunized children showed an increased incidence of RSV lower respiratory tract disease and developed abnormally severe illnesses, including death.

Chemotherapy with ribavirin [1-beta-D-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide], an antiviral nucleoside which is the only pharmaceutical approved by the U.S. Food and Drug Administration (FDA) for treatment of RSV disease, is considered only for certain RSV patients (e.g., those at high risk for severe complications or who are seriously ill with this infection). However, its efficacy and value are controversial. Recent studies have reported a failure to demonstrate either clinical or economic benefit to patients on ribavirin treatment. Moreover, ribavirin has certain toxic side-effects and, in order to minimize these, must be administered by inhalation as an aerosol in an enclosed environment.

A human intravenous immune globulin (IVIG) preparation is licensed for prophylactic use in certain patients at high-risk for RSV disease. Administration of this drug requires intravenous infusion of a large volume over a 2 to 4 hour period in children who have limited venous access due to prior intensive therapy, as well as compromised cardiopulmonary function. Moreover, intravenous infusion necessitates monthly hospital visits during the RSV season, which in turn places children at risk of nosocomial infections.

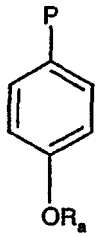
Thus, a need exists for new anti-viral agents and treatments for RSV infection that overcome the shortcomings of existing pharmaceutical preparations.

International Patent Application No. PCT/US99/01985 (filed on January 29, 1999), now published as WO 99/38508, teaches certain dialdehyde compounds to be useful as an intermediate for making certain useful antiviral compounds, and is hereby expressly incorporated-by-reference in its entirety.

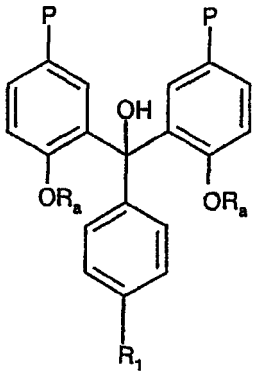
SUMMARY OF THE INVENTION

It has now unexpectedly been discovered that various 4,4'-dihydroxy-3,3'-(4-substituted-phenyl)methylenebisbenzaldehydes, which are useful intermediates for the preparation of compounds exhibiting antiviral activity against RSV, can be made advantageously by novel methods from novel precursor compounds.

The aforementioned intermediates can be made from compounds of Formula I and Formula II (below):



(I)



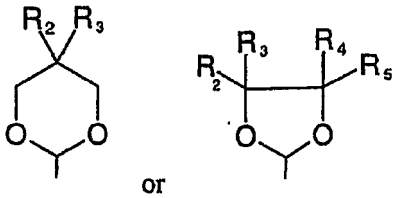
(II)

wherein R_a is selected from the group consisting of $-CH_2-OCH_3$, $-CH_2-OCH_2CH_3$, $-CH(CH_3)OCH_2CH_3$, $-CH_2-OCH_2CH_2-OCH_3$, $-CH_2OCH_2CH_2-Si(CH_3)_3$, and


;

R_1 is a radical selected from the group consisting of hydrogen, halogen, perfluoroalkyl, nitro, carbalkoxy, carboxamide, carboxamidoalkyl, alkyl, cycloalkyl, alkoxy, alkoxyalkyl, alkoxy-C_2-C_6-alkoxy, alkylsulfinyl, alkylsulfonyl, sulfonamide, cyano, amido, dialkylamino, OR_a, or a heterocyclic radical selected from the group consisting of morpholinyl, piperadinyl, pyrrolidinyl, or an N-substituted piperazinyl, said piperazinyl substituents selected from an alkyl group, the point of attachment of said heterocyclic radical is at a nitrogen atom;

P is a protected formaldehyde group such as:



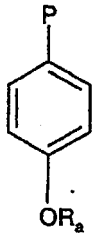
or

wherein R_2, R_3, R_4 and R_5 are independently selected from the group consisting of hydrogen or alkyl.

The invention also relates to methods of making the compounds of Formula I and Formula II and methods of using such compounds in the preparation of antiviral compounds.

DETAILED DESCRIPTION OF THE INVENTION

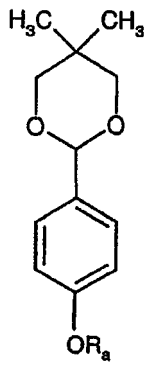
In one aspect, the instant invention provides the compound of Formula I:



(I)

wherein P and R_a are as defined above.

A preferred aspect of the invention includes the compound of Formula Ia having the formula:

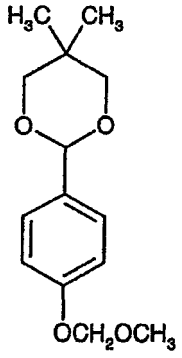


(Ia)

wherein R_a is as defined above.

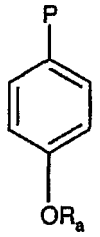
Another preferred aspect of the invention involves the compound of Formula I wherein R_a is $-CH_2-OCH_3$.

An ultimately preferred compound of the invention is that having the formula:

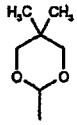
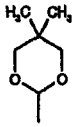
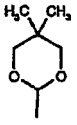
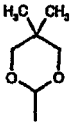
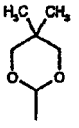
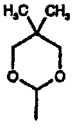
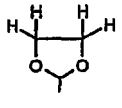


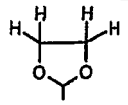
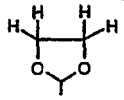
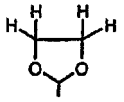
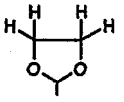
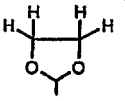
Preferred compounds include compounds of Table 1:

TABLE 1

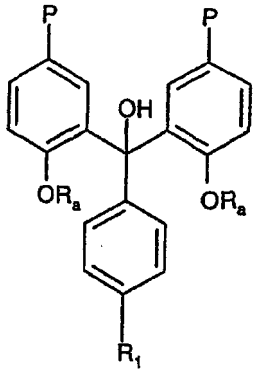


(I)

Compound Number	P	R_a
1		$-CH_2-OCH_3$
2		$-CH_2-OCH_2CH_3$
3		$-CH(CH_3)OCH_2CH_3$
4		$-CH_2-OCH_2CH_2-OCH_3$
5		$-CH_2OCH_2CH_2-Si(CH_3)_3$
6		
7		$-CH_2-OCH_3$

Compound Number	P	R_a
8		$-CH_2-OCH_2CH_3$
9		$-CH(CH_3)OCH_2CH_3$
10		$-CH_2-OCH_2CH_2-OCH_3$
11		$-CH_2OCH_2CH_2-Si(CH_3)_3$
12		

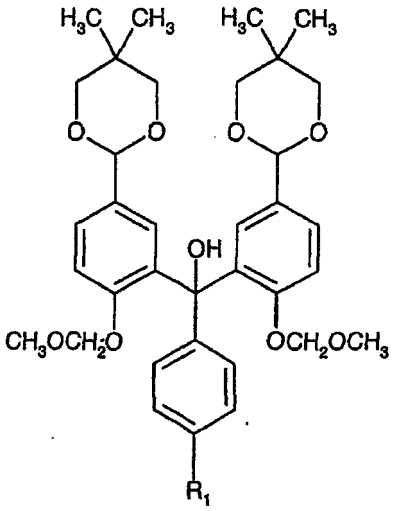
Another aspect of the present invention is the compound of Formula II:



(II)

wherein P, R_1, and R_a are as defined above.

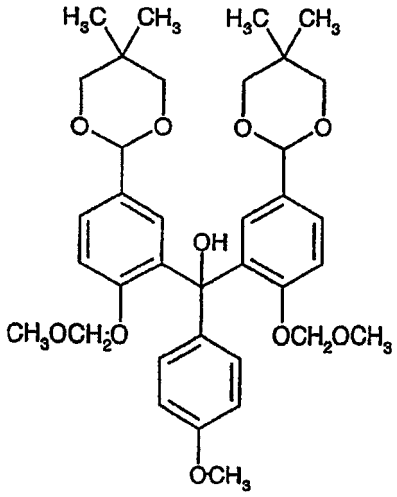
A preferred aspect of the invention includes the compound of Formula II having the formula:



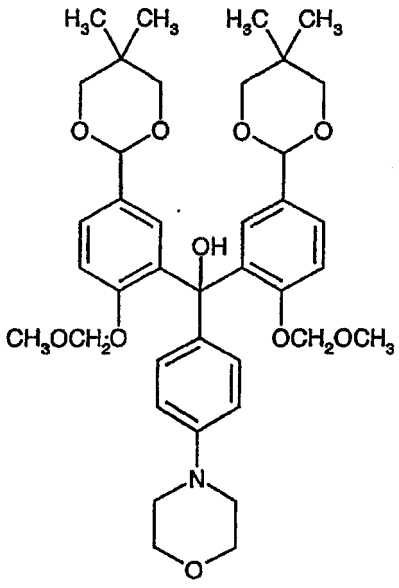
(IIa)

wherein R_1 is as defined above.

Preferred compounds of Formula II include:



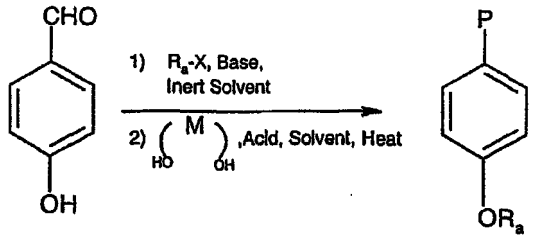
and



Further aspects of the invention are the methods of preparing the compounds of Formula I and II. The compound of Formula I may be prepared according to the following Schemes:

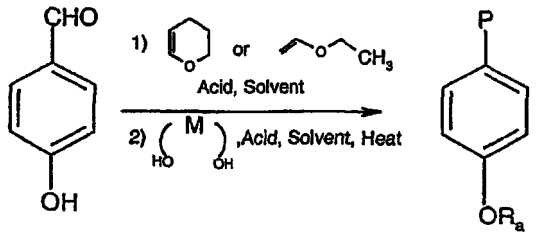
SCHEME 1

M= $(CH_2-CR_2R_3-CH_2)$ or $(CR_2R_3-CR_4R_5)$ wherein R_2, R_3, R_4 and R_5 are defined above; and R_a is as defined above.



(1a)

(I)



(1b)

(I)

The 4-hydroxybenzaldehyde starting material in Scheme 1 is known and readily available from commercial sources. The order of the protection conditions used for the preparation of the di-protected compound of Formula I may be reversed, and the single-protected intermediates prepared therein may be isolated and/or purified if desired prior to preparation of the compound of Formula I.

Scheme (1a) involves the reaction of 4-hydroxybenzaldehyde with an appropriate R_a-X reagent, wherein X is chloride, bromide, or iodide, in the presence of a base such as

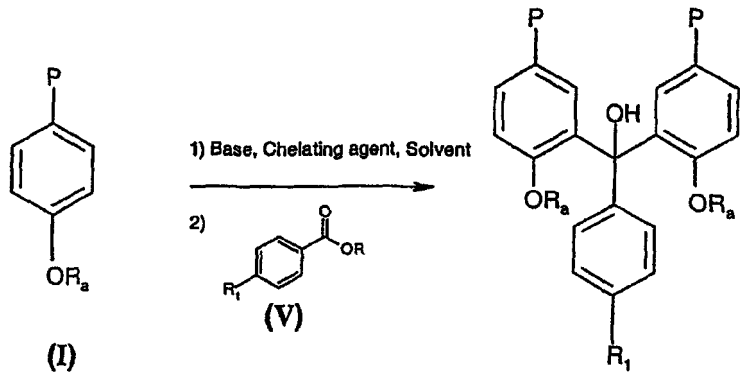
diisopropylethylamine, triethylamine, potassium carbonate, sodium hydride, or pyridine; and in an inert solvent. Depending on the base, a preferable inert solvent may be one or more of the following: dichloromethane, tetrahydrofuran, 1-methyl-2-pyrrolidinone, dimethyl sulfoxide, acetone, or N,N-dimethylformamide; at temperatures ranging from -20°C to 100°C. For example, Scheme (1a) would be amenable to making compounds of Formula I wherein R_a is $-CH_2OCH_3$, $-CH_2OCH_2CH_3$, $-CH_2-OCH_2CH_2-OCH_3$, or $-CH_2-OCH_2CH_2-Si(CH_3)_3$. The aldehyde is protected by refluxing with the appropriate glycol in the presence of an acid, e.g., pyridinium para-toluenesulfonate, pyridinium hydrochloride, *p*-toluenesulfonic acid monohydrate, camphorsulfonic acid, and Amberlyst®-15; and in an inert solvent, such as benzene, toluene, cyclohexane or tetrahydrofuran, preferably with the azeotropic removal of water. The acid is preferably a mild acid and/or preferably used in a catalytic amount.

Scheme (1b) involves the reaction of 4-hydroxybenzaldehyde with dihydropyran in the case where R_a is  or with ethyl vinyl ether in the case where R_a is $-CH(CH_3)OCH_2CH_3$ in the presence of an acid catalyst, such as pyridinium para-toluenesulfonate, dry hydrochloric acid, pyridinium hydrochloride, camphorsulfonic acid, Amberlyst®-15, or *p*-toluenesulfonic acid monohydrate; and in a non-polar inert solvent, such as methylene chloride, ethyl acetate, dimethyloxyethane, dioxane, chloroform, dichloroethane, or tetrahydrofuran; at temperatures between -20°C and 140°C, or otherwise above the freezing point and up to the reflux temperature of the solvent. The aldehyde is protected as above in Scheme (1a).

The compound of Formula II may be prepared according to the following Scheme:

SCHEME 2

P, R_a and R_1 are as defined above; R is an alkyl group; and Solvent = aprotic solvent such as tetrahydrofuran.

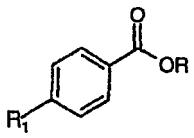


The compounds of Formula II may be prepared in general by treating the compound of Formula I with one or more known alkali metal bases, such as *n*-butyllithium, *sec*-butyllithium, and *t*-butyllithium, or a metal amide base, such as lithium diisopropylamide; preferably in the presence of a chelating agent, such as N,N,N',N'-tetramethylethylenediamine (TMEDA) or hexamethylphosphoramide (HMPA); followed by the addition of an alkyl ester of the appropriate 4-substituted benzoic acid (Formula V) that corresponds to the desired product of Formula II. The reaction may be conducted preferably in the presence of an aprotic organic solvent, such as tetrahydrofuran, 2-methyltetrahydrofuran, diethylether, or *t*-butyl methyl ether, and preferably at reduced temperatures, e.g. between -70°C and room temperature. It is also preferable to conduct the reaction under anhydrous or substantially anhydrous conditions.

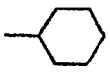
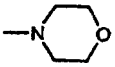
The compounds of Formula V may be purchased from commercial sources or alternatively are readily synthesized by standard procedures which are well know to those of ordinary skill in the art.

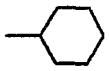
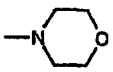
Preferred compounds of Formula V include compounds of Table 2:

TABLE 2



(V)

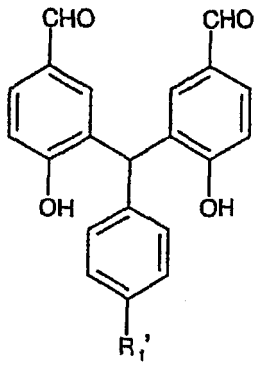
Compound Number	R	R_1
13	CH_3	OCH_2OCH_3
14	CH_3	F
15	CH_3	Cl
16	CH_3	Br
17	CH_3	CF_3
18	CH_3	$CH_2CH_2CH_3$
19	CH_3	$N(CH_3)_2$
20	CH_3	CH_2CF_3
21	CH_3	$CH(CH_3)_2$
22	CH_3	CH_3
23	CH_3	OCH_3
24	CH_3	OCH_2CH_3
25	CH_3	$CH_2CH(CH_2CH_3)_2$
26	CH_3	
27	CH_3	$CH_2CH_2CH_2CH_3$
28	CH_3	$CH_2CH_2CH_2CH_2CH_3$
29	CH_3	$CH(CH_3)CH_2CH_3$
30	CH_3	$CH_2CH(CH_3)_2$
31	CH_3	$CH_2CH_2OCH_3$
32	CH_3	CH_2CH_3
33	CH_3	

Compound Number	R	R_1
34	CH_3	NO_2
35	CH_3	$OCH_2CH_2OCH_3$
36	CH_3	$N(CH_2CH_3)(CH_2CH_2CH_3)$
37	CH_2CH_3	OCH_2OCH_3
38	CH_2CH_3	F
39	CH_2CH_3	Cl
40	CH_2CH_3	Br
41	CH_2CH_3	CF_3
42	CH_2CH_3	$CH_2CH_2CH_3$
43	CH_2CH_3	$N(CH_3)_2$
44	CH_2CH_3	CH_2CF_3
45	CH_2CH_3	$CH(CH_3)_2$
46	CH_2CH_3	CH_3
47	CH_2CH_3	OCH_3
48	CH_2CH_3	OCH_2CH_3
49	CH_2CH_3	$CH_2CH(CH_2CH_3)_2$
50	CH_2CH_3	
51	CH_2CH_3	$CH_2CH_2CH_2CH_3$
52	CH_2CH_3	$CH_2CH_2CH_2CH_2CH_3$
53	CH_2CH_3	$CH(CH_3)CH_2CH_3$
54	CH_2CH_3	$CH_2CH(CH_3)_2$
55	CH_2CH_3	$CH_2CH_2OCH_3$
56	CH_2CH_3	CH_2CH_3
57	CH_2CH_3	
58	CH_2CH_3	NO_2
59	CH_2CH_3	$OCH_2CH_2OCH_3$
60	CH_2CH_3	$N(CH_2CH_3)(CH_2CH_2CH_3)$
61	CH_2CH_3	$C(O)\text{-}OC(CH_3)_3$

Compound Number	R	R_1
62	CH_2CH_3	$C(O)\text{-}OC_2H_5$

Preferred compounds of Formula II can be prepared by reacting the compounds of Table 1 with compounds of Table 2 under the reaction conditions of Scheme 2.

Another feature of the invention is the method of preparing the dialdehyde compound of Formula III:



(III)

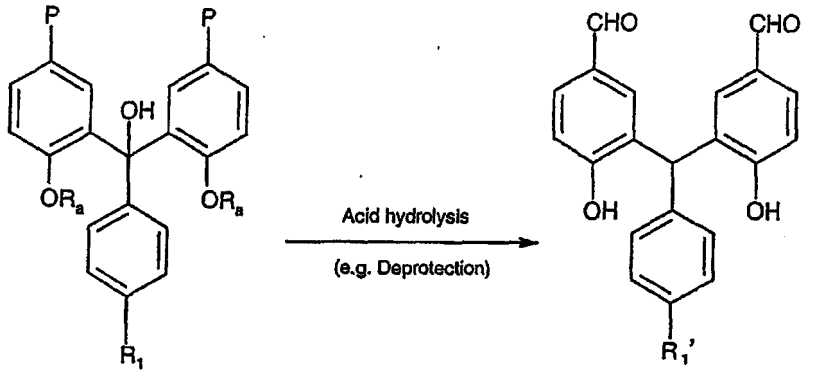
wherein R_i' is a radical selected from the group consisting hydrogen, hydroxy, halogen, perfluoroakyl, nitro, carbalkoxy, carboxamide, carboxamidoalkyl, alkyl, alkoxy, alkoxyalkyl, alkoxy-C_2-C_6-alkoxy, cycloalkyl, alkylsulfinyl, alkylsulfonyl, sulfonamide, cyano, amido, dialkylamino, or a heterocyclic radical selected from the group consisting of morpholinyl, piperadinyl, pyrrolidinyl, or an N-substituted piperazinyl, said piperazinyl substituents selected from an alkyl group, the point of attachment of said heterocyclic radical is at a nitrogen atom.

The compounds of Formula III are useful for preparing antiviral compounds described in International Patent Application No. PCT/US99/01985 (filed on January 29, 1999), now published as WO 99/38508.

The compound of Formula III may be prepared according to the following Scheme 3 below.

SCHEME 3

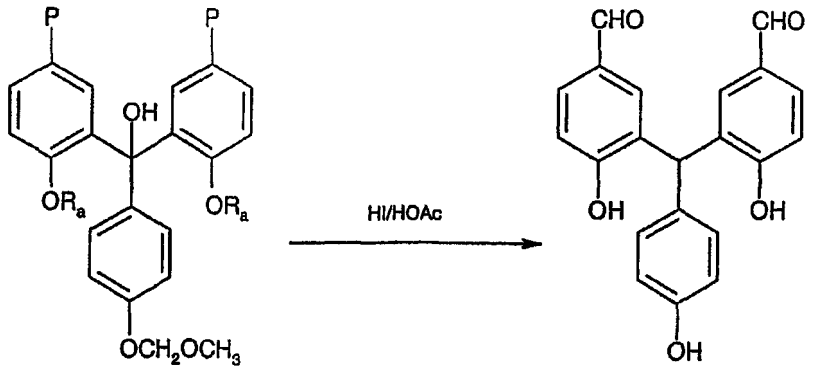
Acid Hydrolysis = treatment with deprotection conditions such as hydriodic acid (HI) and acetic acid (HOAc); and R_a R_1, P and R_1' are as defined above.



(II) **(III)**

Reduction and regeneration of the aldehyde is achieved under certain acidic conditions, such as hydriodic acid in acetic acid, preferably at room temperature; to form the dialdehyde intermediate of Formula III. The compounds of Formula III are not co-extensive with compounds of Formula II because the compounds of Formula II where R_1 is OR_a will not survive the reaction conditions and will undergo deprotection to form R_1'.

A preferred aspect of the invention is the process of preparing the compound of Formula III, wherein R_1' is –OH from compounds of Formula II wherein R_1 is an OR_a group, by treating compounds of Formula II with hydriodic acid in acetic acid, preferably at room temperature:

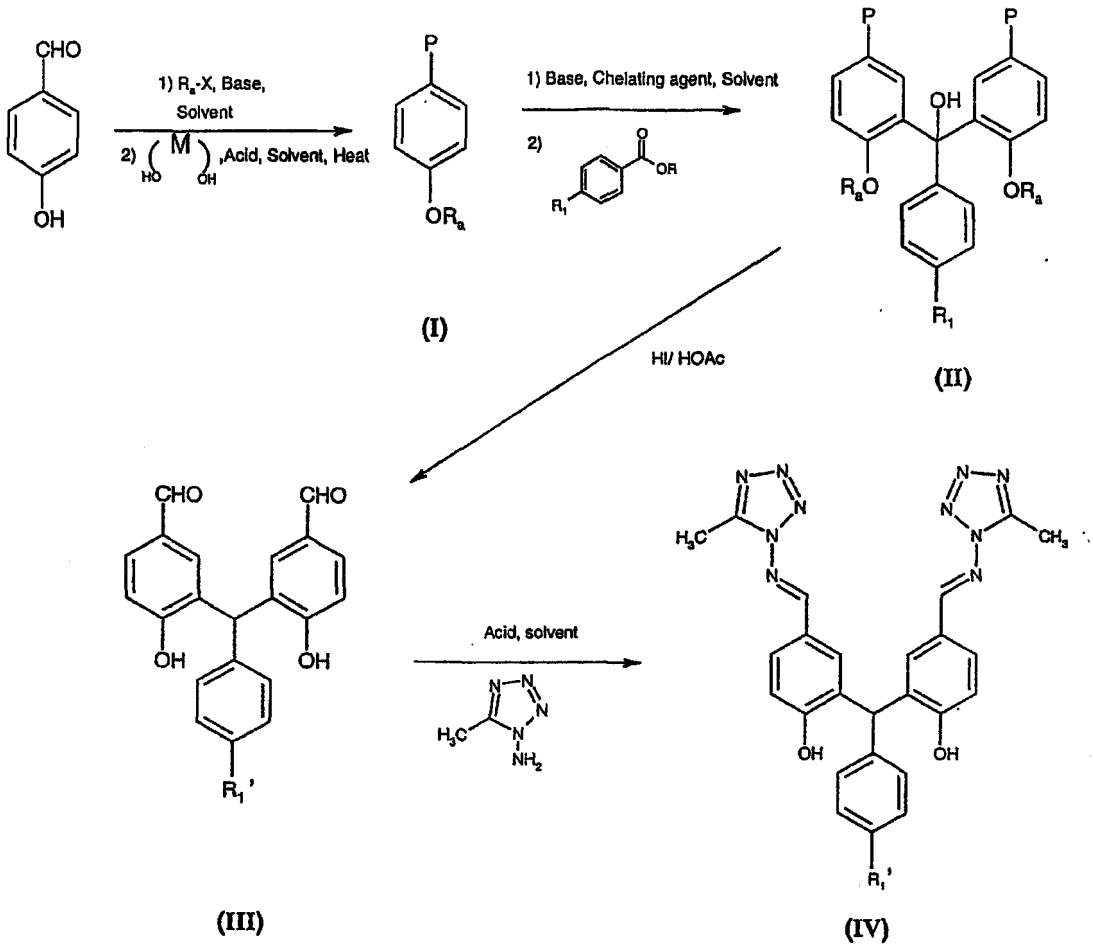


A feature of the instant invention includes the methods of making certain antiviral compounds disclosed in International Patent Application No. PCT/US99/01985 from the compounds of Formula I and/or II using the corresponding methods of making disclosed herein.

Scheme 4 illustrates an aspect of the invention regarding a method of preparing the antiviral compound of Formula IV:

SCHEME 4

HI = hydriodic acid; HOAc = acetic acid; and P, M, R_1, R_1', R, and R_a are as defined above.



The last step involves the condensation of the aldehyde groups with 5-methyl-1H-tetrazolamine, in the presence of an acid, such as *p*-toluenesulfonic acid monohydrate, methanesulfonic acid, benzenesulfonic acid, or pyridinium para-toluenesulfonate, at elevated temperatures, e.g. from room temperature to 90°C; in a solvent such as an alcoholic solvent like ethanol, or in 1-methyl-2-pyrrolidinone, dimethyl sulfoxide, or N,N-dimethylformamide; to provide the antiviral compound of Formula IV. The compounds of Formula IV are useful for treating and preventing disease caused by *Pneumovirnae* viruses, preferably human respiratory syncytial virus (RSV).

The term "alkyl", as used herein, refers to aliphatic hydrocarbon radicals of one to six carbon atoms in length. Similarly, the term "alkyl", or any variation thereof, used in combination form to name substituents, such as alkoxy (-O-alkyl), alkylthio (-S-alkyl), alkylamino (-NH-alkyl), alkylsulfinyl (-S(O)-alkyl), alkylsulfonyl (-$S(O)_2$-alkyl),

carboxamidoalkyl (-alkyl-C(=O)-NR″R‴), or the like, also refers to aliphatic hydrocarbon radicals of one to six carbon atoms in length, and preferably of one to four carbon atoms in length.

The term "amido", as used herein, refers to a radical or substituent of the formula -NR″C(=O)R‴, wherein R″ and R‴ represent alkyl.

The term "carboxamide", as used herein, refers to a radical or substituent of the formula -C(=O)-NR″R‴, wherein R″ and R‴ are as previously defined.

The term "sulfonamide", as used herein, refers to a radical or substituent of the formula -SO_2NR″R‴ or -NR″SO_2R‴, wherein R″ and R‴ are as previously defined.

The term "carbalkoxy", as used herein, refers to a radical or substituent -C(=O)-OR″, wherein R″ is a previously defined.

The following examples are provided to describe the invention in further detail. These examples, which set forth the preferred mode presently contemplated for carrying out the invention, are intended to illustrate and not to limit the invention.

Examples 1-5 illustrate suitable methods of synthesis of representative compounds of this invention. However, the methods of synthesis are not limited to those exemplified below.

EXAMPLE 1

2-(4-Methoxymethoxyphenyl)-5,5-dimethyl-1,3-dioxane

(a) 4-Methoxymethoxybenzaldehyde: 4-Hydroxybenzaldehyde (10.04 g, 87.2 mmol) was dissolved in 160 ml of methylene chloride and 28.0 ml of N,N-diisopropylethylamine, under argon. The solution was cooled to 0 °C, and chloromethyl methyl ether (8.1 ml, 107 mmol) was added. After the addition, the solution was warmed to room temperature, and then stirred for 2 hours. The reaction was quenched with water, and the aqueous phase was separated from the organic phase. The aqueous phase was further extracted two times with methylene chloride, and the combined organic layers were washed with saturated aqueous NaCl. The solution was dried with sodium sulfate, filtered, and rotary evaporated. The product was taken directly to next step.

(b) 2-(4-Methoxymethoxyphenyl)-5,5-dimethyl-1,3-dioxane:

4-Methoxymethoxybenzaldehyde from step (a) above, neopentyl glycol (10.3 g, 98.9 mmol), and pyridinium para-toluenesulfonate (1.0 g, 3.98 mmol) were dissolved in 500 ml of benzene. The flask was equipped with a Dean-Stark trap, and the reaction was heated to reflux for several hours, under argon with azeotropic removal of water. The reaction was cooled to room temperature, quenched with 2 ml of triethylamine, and concentrated on rotary evaporator. The product was chromatographed on silica with a gradient of 5% ethyl acetate in hexanes, yielding 10.95 g of clean product.

EXAMPLE 2

5,5'-Bis (5,5-dimethyl-1,3-dioxan-2-yl)-4''-methoxy-2,2'-bis(methoxymethoxy)triphenylmethanol

2-(4-Methoxymethoxyphenyl)-5,5-dimethyl-1,3-dioxane (5.02 g, 19.9 mmol) was dissolved in 65 ml of distilled tetrahydrofuran in a 3-neck flask, under argon. N,N,N',N'-Tetramethylethylenediamine (3.0 ml, 19.9 mmol) was added to the solution, and the resulting mixture was stirred at 0 °C in an ice/NaCl bath. Sec-butyllithium (16.8 ml, 1.3 M in cyclohexane) was added via a syringe pump at the rate of 0.25ml/min, maintaining the reaction at a constant temperature. The solution was stirred for 15 minutes, then a second solution of methyl 4-methoxybenzoate (1.10 g, 6.62 mmol) in 25 ml distilled tetrahydrofuran was added drop wise to the reaction. After this addition, the solution was stirred for 2 hours at 0 °C. The reaction was then quenched with half-saturated aqueous NH_4Cl solution. The organic solvents were removed *in vacuo*, and the aqueous mixture was extracted three times with ethyl acetate. The organic layers were combined, washed with saturated aqueous NaCl, dried with sodium sulfate, filtered, and concentrated on rotary evaporator. The residue was chromatographed on silica with a gradient of 20-30 % ethyl acetate in hexanes, yielding 3.55 g of desired product as a solid, white foam.

EXAMPLE 3

4,4'-dihydroxy-3,3'-(4-methoxyphenyl)methylenebisbenzaldehyde

5,5'-Bis (5,5-dimethyl-1,3-dioxan-2-yl)-4''-methoxy-2,2'-bis(methoxymethoxy)triphenylmethanol (0.998 g, 1.56 mmol) was dissolved in 16 ml of glacial acetic acid. Hydriodic acid (2.6 ml, 57 wt % in water) was added in one portion, turning the solution brown. The reaction was stirred at room temperature overnight, under argon.

The reaction mixture was diluted with 200 ml of water and extracted three times with ethyl acetate. The organic layers were combined and washed with saturated aqueous $NaHSO_3$ (200 ml). The solution was dried over sodium sulfate, rotary evaporated, and further dried under vacuum. The resulting brown solid was heated and sonicated in 50 ml of ethyl acetate, then cooled to room temperature. The remaining solid was collected by filtration, rinsed with ethyl acetate, and dried under vacuum, yielding 321.1 mg of product.

EXAMPLE 4

α,α-Bis-[5-(5,5-dimethyl-1,3-dioxan-2-yl)-2-(methoxymethoxy)phenyl]-α-[4-(4-morpholinyl)phenyl]methanol

(a) 4-(4-Morpholinyl)benzoic acid ethyl ester: A Schenk flask containing ethyl 4-bromobenzoate (3.39 g, 14.8 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.136 g, 0.148 mmol), (S)-binaphthol (0.138 g, 0.222 mmol), and cesium carbonate (6.79 g, 20.8mmol) was evacuated by vacuum and filled with argon. Morpholine (1.55 g, 17.8 mmol, distilled from KOH) and toluene (50 ml) were added to the flask. The reaction vessel was then closed and heated to 100 °C for 24 hours. The reaction mixture was cooled to room temperature, diluted with water, and extracted with ether (3x). The mixture was washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude product was purified via column chromatography (silica gel, 50 % ethyl acetate in hexanes) to provide 0.67 g product.

(b) α,α-Bis-[5-(5,5-dimethyl-1,3-dioxan-2-yl)-2-(methoxymethoxy)phenyl]-α-[4-(4-morpholinyl)phenyl]methanol: 2-(4-Methoxymethoxyphenyl)-5,5-dimethyl-1,3-dioxane, prepared according to Example 1-b, above (2.05 g, 8.14 mmol) was mixed with N,N,N',N'-tetramethylethylenediamine (0.95 g, 8.14 mmol) and tetrahydrofuran (27 ml).

The mixture was cooled to 0°C in a NaCl/ice mixture bath. Sec-butyllithium (6.9 ml of 1.3 M in cyclohexane, 8.95 mmol) was added dropwise, maintaining the reaction temperature below 0°C. After stirring for 15 minutes, 4-(4-morpholinyl)benzoic acid ethyl ester, prepared in step a, above (0.60 g, 2.55 mmol) dissolved in tetrahydrofuran (15 ml) was added dropwise to the reaction mixture. The reaction was slowly warmed to room temperature and stirred overnight. The reaction was quenched with 10% NH_4Cl solution, and the tetrahydrofuran was removed on rotary evaporator. The remaining solution was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*, to provide 0.63 g of desired product.

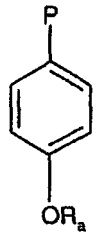
EXAMPLE 5

3,3'-[[4-(4-morpholinyl)phenyl]methylene]bis-4-hydroxybenzaldehyde

Hydriodic acid (0.58 ml, 58 wt % in water) was added to a solution of α,α-Bis-[5-(5,5-dimethyl-1,3-dioxan-2-yl)-2-(methoxymethoxy)phenyl]-α-[4-(4-morpholinyl)phenyl]methanol prepared according to Example 4, (0.40 g, 0.58 mmol) in glacial acetic acid (5.8 ml). The reaction was stirred at room temperature for 2 hours. The reaction mixture was poured over ice/water, and 10% aqueous $NaHSO_3$ was added. The mixture was extracted with ethyl acetate, and the organic layer was washed with 10% aqueous $NaHSO_3$ and saturated aqueous NaCl solution. The organics were dried over magnesium sulfate, filtered, and rotary evaporated. The resulting solid was recrystallized in ethyl acetate/hexanes, than further purified via column chromatography (silica gel, ethyl acetate/hexanes) to provide 38.7 mg of desired product.

WHAT IS CLAIMED IS:

1. A compound having the formula:

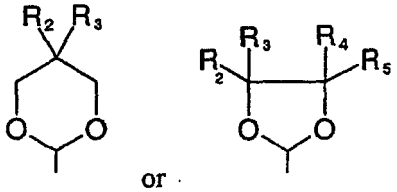


(I)

wherein R_a is selected from the group consisting of $-CH_2-OCH_3$, $-CH_2-OCH_2CH_3$, $-CH(CH_3)OCH_2CH_3$, $-CH_2-OCH_2CH_2-OCH_3$, $-CH_2OCH_2CH_2-Si(CH_3)_3$, and

;

and P is a protected formaldehyde group selected from the group of:

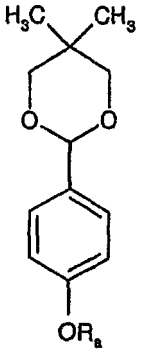


or

wherein R_2, R_3, R_4 and R_5 are independently selected from the group consisting of hydrogen or alkyl.

2. A compound according to claim 1 wherein R_a is $-CH_2-OCH_3$.

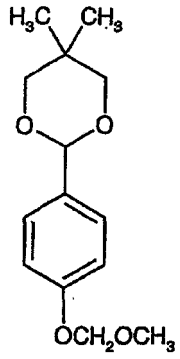
3. A compound according to claim 1 having the formula:



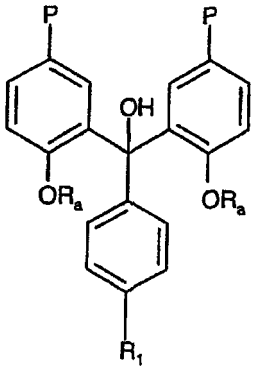
(Ia)

wherein R_a is selected from the group consisting of $-CH_2-OCH_3$, $-CH_2-OCH_2CH_3$, $-CH(CH_3)OCH_2CH_3$, $-CH_2-OCH_2CH_2-OCH_3$, $-CH_2OCH_2CH_2-Si(CH_3)_3$, and

4. The compound according to claim 1 having the formula:



5. A compound having the formula:



(II)

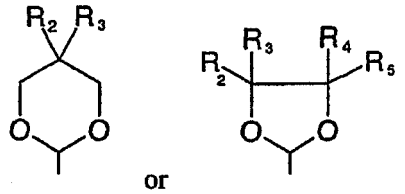
wherein R_a is selected from the group consisting of $-CH_2-OCH_3$, $-CH_2-OCH_2CH_3$, $-CH(CH_3)OCH_2CH_3$, $-CH_2-OCH_2CH_2-OCH_3$, $-CH_2OCH_2CH_2-Si(CH_3)_3$, and


;

R_1 is a radical selected from the group consisting of hydrogen, halogen, perfluoroalkyl, nitro, carbalkoxy, carboxamide, carboxamidoalkyl, alkyl, cycloalkyl,

alkoxy, alkoxyalkyl, alkoxy-C_2-C_6-alkoxy, alkylsulfinyl, alkylsulfonyl, sulfonamide, cyano, amido, dialkylamino, OR_a, or a heterocyclic radical selected from the group consisting of morpholinyl, piperadinyl, pyrrolidinyl, or an N-substituted piperazinyl, said piperazinyl substituents selected from an alkyl group, the point of attachment of said heterocyclic radical is at a nitrogen atom.

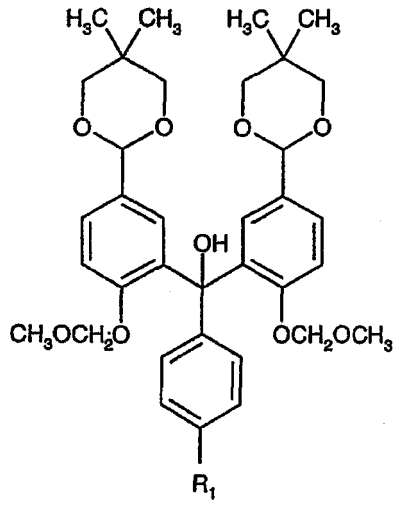
P is a protected formaldehyde group selected from the group of:



or

wherein R_2, R_3, R_4 and R_5 are independently selected from the group consisting of hydrogen or alkyl.

6. A compound according to claim 5 having the formula:

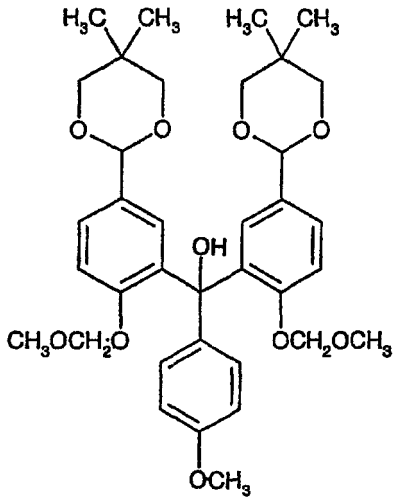


(IIa)

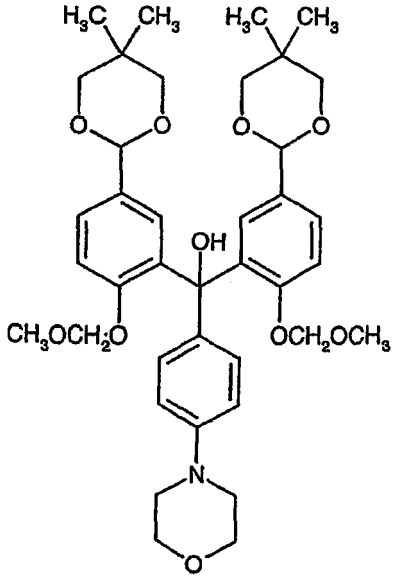
wherein R_1 is a radical selected from the group consisting of hydrogen, halogen, perfluoroalkyl, nitro, carbalkoxy, carboxamide, carboxamidoalkyl, alkyl, cycloalkyl, alkoxy, alkoxyalkyl, alkoxy-C_2-C_6-alkoxy, alkylsulfinyl, alkylsulfonyl, sulfonamide, cyano, amido, dialkylamino, OR_a, or a heterocyclic radical selected from the group

consisting of morpholinyl, piperadinyl, pyrrolidinyl, or an N-substituted piperazinyl, said piperazinyl substituents selected from an alkyl group, the point of attachment of said heterocyclic radical is at a nitrogen atom.

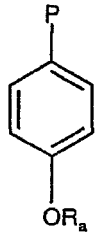
7. The compound according to claim 5 having the formula:



8. The compound according to claim 5 having the formula:



9. The process of preparing the compound having the formula:

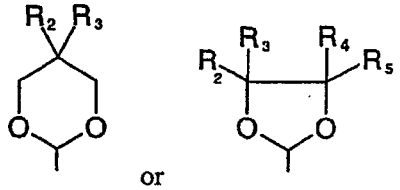


(I)

wherein R_a is selected from the group consisting of $-CH_2-OCH_3$, $-CH_2-OCH_2CH_3$, $-CH(CH_3)OCH_2CH_3$, $-CH_2-OCH_2CH_2-OCH_3$, $-CH_2OCH_2CH_2-Si(CH_3)_3$, and

;

and P is a protected formaldehyde group selected from the group of:



or

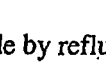
wherein R_2, R_3, R_4 and R_5 are independently selected from the group consisting of hydrogen or alkyl, said process comprising the process steps of:

a) protecting the hydroxy group of the 4-hydroxybenzaldehyde by:

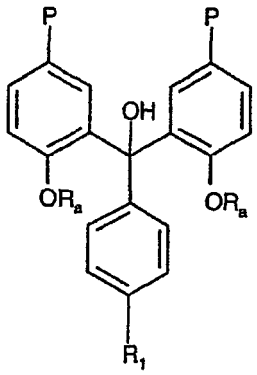
i) treating 4-hydroxybenzaldehyde with R_a-X in the presence of a base in an inert solvent, wherein X is chloride, bromide, or iodide; and wherein R_a is $-CH_2OCH_3$, $-CH_2OCH_2CH_3$, $-CH_2-OCH_2CH_2-OCH_3$, or $-CH_2-OCH_2CH_2-Si(CH_3)_3$; or

ii) reacting 4-hydroxybenzaldehde with dihydropyran in the case where R_a is

or with ethyl vinyl ether in the case where R_a is $-CH(CH_3)\ OCH_2CH_3$, in a non-polar inert solvent, in the presence of an acid; and

b) protecting the aldehyde by refluxing the product of step a) with  , wherein M is (CH_2– CR_2R_3 – CH_2) or (CR_2R_3 – CR_4R_5), wherein R_2, R_3, R_4 and R_5 are as defined above; in the presence of an acid, and in an inert solvent.

10. The process of preparing the compound having the formula:



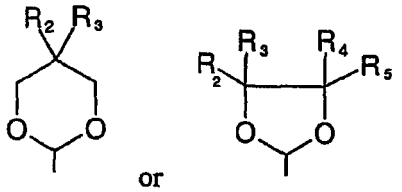
(II)

wherein R_a is selected from the group consisting of -CH_2-OCH_3, -CH_2-OCH_2CH_3, -$CH(CH_3)OCH_2CH_3$, -CH_2-OCH_2CH_2-OCH_3, -$CH_2OCH_2CH_2$-$Si(CH_3)_3$, and

;

R_1 is a radical selected from the group consisting of hydrogen, halogen, perfluoroalkyl, nitro, carbalkoxy, carboxamide, carboxamidoalkyl, alkyl, cycloalkyl, alkoxy, alkoxyalkyl, alkoxy-C_2-C_6-alkoxy, alkylsulfinyl, alkylsulfonyl, sulfonamide, cyano, amido, dialkylamino, OR_a, or a heterocyclic radical selected from the group consisting of morpholinyl, piperadinyl, pyrrolidinyl, or an N-substituted piperazinyl, said piperazinyl substituents selected from an alkyl group, the point of attachment of said heterocyclic radical is at a nitrogen atom;

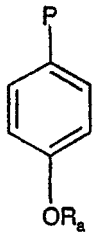
P is a protected formaldehyde group selected from the group of:



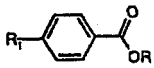
or

wherein R_2, R_3, R_4 and R_5 are independently selected from the group consisting of hydrogen or alkyl,

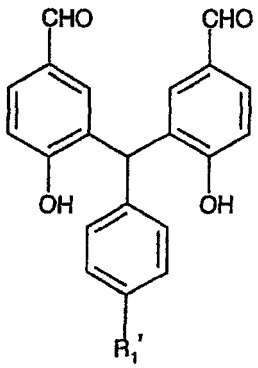
said process comprising the step of treating a compound of Formula I:



(I)

with an alkali metal base or a metal amide base, and with an alkyl ester of a substituted benzoic acid having the formula  wherein R is alkyl.

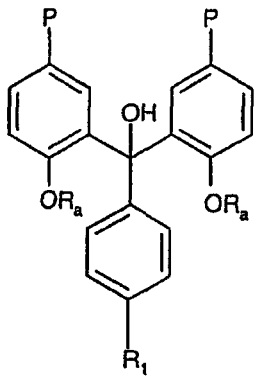
11. The process of preparing the compound having the formula:



(III)

wherein R_1' is a radical selected from the group consisting hydrogen, hydroxy, halogen, perfluoroakyl, nitro, carbalkoxy, carboxamide, carboxamidoalkyl, alkyl, alkoxy, alkoxyalkyl, alkoxy-C_2-C_6-alkoxy, cycloalkyl, alkylsulfinyl, alkylsulfonyl, sulfonamide, cyano, amido, dialkylamino, or a heterocyclic radical selected from the group consisting of morpholinyl, piperadinyl, pyrrolidinyl, or an N-substituted piperazinyl, said piperazinyl substituents selected from an alkyl group, the point of attachment of said heterocyclic radical is at a nitrogen atom;

said process comprising the step of treating a compound of Formula II:



(II)

wherein R_1 is a radical selected from the group consisting of hydrogen, halogen, perfluoroalkyl, nitro, carbalkoxy, carboxamide, carboxamidoalkyl, alkyl, cycloalkyl, alkoxy, alkoxyalkyl, alkoxy-C_2-C_6-alkoxy, alkylsulfinyl, alkylsulfonyl, sulfonamide, cyano, amido, dialkylamino, OR_a, or a heterocyclic radical selected from the group consisting of morpholinyl, piperadinyl, pyrrolidinyl, or an N-substituted piperazinyl, said piperazinyl substituents selected from an alkyl group, the point of attachment of said heterocyclic radical is at a nitrogen atom;

with hydriodic acid in acetic acid.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/02338

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07F 7/02; C07D 317/00, 319/06, 407/00, 413/00; C07C 45/00, 47/56
US CL : 549/214, 370, 374, 414, 453; 544/148; 568/435, 442

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 549/214, 370, 374, 414, 453; 544/148; 568/435, 442

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 319947 A2 (GREEN CROSS CORP.) 14 June 1989 page 2 lines 30-52.	1,2

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 April 2002 (30.04.2002)	05 JUN 2002
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Valerie Bell-Harris for Amelia A. Owens Telephone No. 703-308-1235

Form PCT/ISA/210 (second sheet) (July 1998)